



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/BE96/00002 <b>(22) International Filing Date:</b> 10 January 1996 (10.01.96) <b>(30) Priority Data:</b> 08/370,883 10 January 1995 (10.01.95) US <b>(71) Applicant (for all designated States except US):</b> GALEPHAR P.R. INC. [VC/PR]; Ave Iturregui Calle B, P.O. Box 3468, Carolina, Puerto Rico 00984-3468 (PR). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DEBOECK, Arthur, M. [BE/PR]; HCO2 Box 14885, Gurabo, Puerto Rico 00778 (PR). BAUDIER, Philippe [FR/BE]; Avenue Blucher 10, B-1410 Waterloo (BE). MAES, Paul, J. [BE/BE]; Rue Robert Ledecq 8, B-1440 Wauthier-Braine (BE). <b>(74) Agents:</b> SCHMITZ, Y. et al.; Gevers Patents, Holidaystraat 5, B-1831 Diegem (BE).	<b>(81) Designated States:</b> AL, AM, AT, AT (Utility model), AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> With international search report.	
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES		
<b>(57) Abstract</b>  A pharmaceutical composition is provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.		

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PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE  
AND POLYGLYCOLIZED GLYCERIDES

BACKGROUND OF THE INVENTION

5 Field of the Invention:

The present invention relates to a pharmaceutical dosage form of fenofibrate having enhanced bioavailability, as well as to an advantageous process for making the same.

Description of the Background:

- 10 Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 300 mg which is administered in two or three doses.
- 15 Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted
- 20 predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate, is presently available in a pharmaceutical dosage form consisting of hard gelatin capsules containing fenofibrate, lactose starch and

25 magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is

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effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity. (Strolin & Al, Act Pharmacol. Toxicol. 1986; 59 (Suppl. 5); 167).

5           The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor and Al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M 1944CS) with HLB of between 3-4. In order to use the  
10 product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in  
15 bioavailability between this liquid formulation and the conventional form when the product was given with food.

European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl  
20 sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrrolidone and magnesium stearate. A formulation of this composition is actually available on the French market  
25 under the trade name Lypantyl 200 M®. A study comparing this formulation (Lypantyl 200 M®) to the conventional form

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was undertaken and a statistically significant increase in bioavailability was indicated for the former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form. (J.L. Suichard & Al Cun Therapeutic Research Vol. 54, NS, Nov. 1993).

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

#### SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a fenofibrate formulation not requiring use of co-micronization which, nevertheless, exhibits a

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bioavailability comparable to formulations of fenofibrate which do.

It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

The above objects and others are provided by a pharmaceutical composition for treating hyperlipidemia in and/or hypercholesterolemia a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a pharmaceutical formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of each of a fenofibrate composition and an excipient which contains one or more polyglycolized glycerides, the polyglycolized glycerides preferably having an HLB value of at least about 10.

The present invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is soluble, whereby particle size specifications are not required.

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The present invention also relates to the addition of a suspension stabilizer to the molten solution of fenofibrate-polyglycolized glycerides. The suspension stabilizer avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene) bloc polymers. Other suspension stabilizers equivalent to these stabilizers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous fenofibrate solution is filled in hard gelatin capsules. This filling process permits the obtention of very precise fenofibrate amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

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Polyglycolized glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean  
5 relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component  
10 contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably  
15 contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire®.

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more  
20 preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18°C and 60°C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30°C, and preferably above 35°C, since there is no need for  
25 sealing the capsule, to assure the leak proofness thereof, when such excipients are used.

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Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The HLB value and melting point of the composition may further be adjusted with the  
5 addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

10 It has also been discovered that the present composition affords an increased bioavailability of the fenofibrate as compared to conventional formulations.

Although the present inventors do not wish to be bound by any particular theories, one plausible mechanism of  
15 operation for the present invention is that upon cooling, the melted mixture of hot fenofibrate-polyglycolized glycerides maintains the fenofibrate in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the  
20 fenofibrate due to the HLB value of the excipient mixture, whereby fenofibrate is readily absorbed.

Generally, the composition of the present invention contains from about 5% to 95% by weight of fenofibrate and from about 95% to 5% by weight of excipient including one  
25 or more polyglycolized glycerides. It is preferred, however, if the present composition contains from about 20%

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to 80% by weight of fenofibrate and from about 80% to 20%  
by weight of excipient. It is even more preferred,  
however, if the present composition contains from about 30%  
to 70% by weight of fenofibrate and from about 70% to 30%  
5 by weight of excipient.

In a particularly preferred composition, generally  
about 45% to 55% by weight of fenofibrate is used and about  
55% to 45% by weight of excipient containing the one or  
more polyglycolyzed glycerides is used.

10 Generally, the method of the present invention entails  
adding one or more excipients, including the one or more  
polyglycolyzed glycerides to containing means and then  
heating the excipients until all components are melted.  
Then, fenofibrate is added slowly with continuous stirring  
15 until all fenofibrate added is dissolved. Stirring is then  
continued for about 10 minutes to about 1 hour, and  
preferably for about 15 minutes to about 30 minutes. Then,  
containing means for the pharmaceutical composition, such  
as hard gelatin capsules, are filled with the composition  
20 using a liquid filing capsule machine having dosing pumps  
which are heated to the same temperature as the temperature  
of the molten pharmaceutical composition. Generally, this  
temperature is about 55°C to about 95°C, more typically in  
the range of about 80°C to 90°C. Upon cooling to ambient  
25 temperature, the capsules are packed in bottles. When

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capsules of size 3 are used, each capsule so prepared contains 67 mg of fenofibrate.

It is advantageous, however, to use the following protocol. To about 3 parts by weight polyglycolized  
5 glyceride excipient having a melting point of 44°C and an HLB value of 14 molten at 80°C, is added about 2 parts by weight of fenofibrate and about 1 part by weight of hydroxypropyl cellulose. After maintaining the solution under agitation for about 20 additional minutes, hard  
10 gelatin capsules are filled therewith.

The present invention will now be further described by reference to certain examples which are provided solely for purposes of illustration and are not intended to be  
limitative.

15

## EXAMPLE 1

Fenofibrate	6.7 kg
Gelucire® 44/14	5.0 kg
Polyoxamer 407	<u>5.0 kg</u>
	16.7 kg

20 In a stainless steel container, were introduced 5 kg of Gelucire® 44/14 and 5 kg of Poloxamer 407, which were then heated at 85°C until all components are molten. 6.7 kg of fenofibrate was added slowly while continuously stirring the mixture. When all of the fenofibrate was  
25 dissolved agitation was maintained for about twenty

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minutes. Using a liquid filing capsule machine with dosing pumps heated at 85°C, capsules of size 3 was filled with 167 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so  
5 prepared contained 67 mg of fenofibrate.

#### PHARMACOKINETICAL STUDY

The composition of Example 1 was compared to conventional form in a pharmacokinetical study with 15 healthy subjects. Each subject received 3 capsules of  
10 composition of Example 1 (201 mg of fenofibrate) or 3 capsules of Lypan tyl 100® (300 mg of the conventional form). The sessions were separated by a wash out period of 7 days. The medications were taken after a high-fat  
breakfast. Blood samples were obtained before and at  
15 different times up to 72 hours after administration. The plasma concentration of fenofibric acid was determined in all available samples using a conventional HPLC method.

Plasma Fenofibric Acid Concentration (mg./l vs. time (h) After Administration at 3 Capsules of Example 1 (Total amount of Fenofibrate administered: 201 mg)															
Post-dose time (h)	1	2	3	4	5	6	8	9	10	11	12	13	14	15	16
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
1	BLOQ	BLOQ	0.42	BLOQ	0.52	0.81	0.29	BLOQ	0.32	BLOQ	BLOQ	BLOQ	BLOQ	0.81	BLOQ
2	0.36	0.34	3.87	4.31	5.10	6.00	4.66	6.46	2.56	BLOQ	BLOQ	BLOQ	3.84	3.03	0.75
3	3.31	1.06	7.52	8.12	12.80	7.68	7.50	7.27	6.55	2.51	3.83	3.22	12.68	6.73	5.62
4	4.06	2.70	6.02	10.87	13.56	8.27	9.42	8.93	8.16	4.46	5.35	5.23	13.93	7.17	9.61
5	4.06	5.49	6.61	10.84	12.65	6.99	9.64	11.70	9.65	6.49	7.42	5.46	14.41	8.53	11.08
6	4.32	7.17	6.42	10.68	12.34	6.32	12.19	16.75	11.64	9.75	12.16	5.76	15.68	9.95	13.70
7	3.82	7.60	4.28	8.50	11.75	5.68	8.93	8.45	11.43	8.89	11.41	3.74	7.60	9.06	10.72
9	4.74	6.83	3.71	6.28	9.61	4.27	8.12	6.19	9.97	6.80	8.79	3.57	7.41	6.42	8.70
12	5.61	8.07	2.36	5.66	8.08	3.49	7.05	4.70	7.78	5.00	7.00	6.25	3.75	4.83	6.49
24	2.57	3.56	0.85	2.48	4.78	1.39	2.51	1.83	3.48	2.19	2.32	2.30	3.67	2.29	2.64
36	1.24	1.53	0.61	1.64	3.01	0.63	1.73	1.16	2.38	1.42	1.64	1.24	1.74	1.26	1.26
48	0.80	0.76	0.27	0.98	2.13	0.29	1.05	0.95	1.54	1.06	1.10	0.63	1.33	0.73	0.88
60	0.55	0.70	BLOQ	0.64	1.43	0.28	0.73	0.43	0.88	0.73	0.92	0.28	0.78	0.48	0.70
72	0.40	0.52	BLOQ	0.50	1.21	BLOQ	BLOQ	0.38	0.68	0.51	0.53	BLOQ	0.62	BLOQ	0.39
														Mean*	SD
														0	-
														0.21	0.30
														2.89	2.19
														6.43	3.37
														7.85	3.33
														8.73	2.99
														10.32	3.71
														8.12	2.71
														6.76	2.05
														5.74	1.73
														2.59	0.97
														1.50	0.61
														0.97	0.47
														0.64	0.33
														0.38	0.34

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Plasma Fenofibric Acid Concentration (mg./l vs. time (h) After Administration at 3 Capsules of the Conventional Form (Total amount of Fenofibrate administered: 300 mg)														
Post- dose time (h)	1	2	3	4	5	6	8	9	10	11	12	13	15	16
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
1	BLOQ	BLOQ	BLOQ	0.25	BLOQ	BLOQ	1.90	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
2	BLOQ	BLOQ	0.25	4.67	0.34	1.52	5.83	BLOQ	BLOQ	0.42	0.63	BLOQ	BLOQ	1.28
3	1.76	0.99	2.16	7.39	4.51	3.72	5.89	2.45	1.53	1.71	1.55	1.03	1.40	3.79
4	3.24	4.62	5.57	9.13	8.83	5.00	5.76	5.12	6.54	4.37	3.58	3.47	1.48	5.08
5	4.53	10.24	12.20	12.16	10.43	4.77	6.57	11.97	12.91	4.93	6.94	4.22	3.55	11.35
6	8.77	17.36	12.93	12.08	13.18	5.66	6.62	14.17	18.00	9.03	11.45	4.30	10.65	17.47
7	4.75	11.92	12.12	10.71	11.36	4.84	5.90	12.31	14.42	8.08	10.58	4.17	10.11	16.35
9	3.64	8.21	9.29	8.39	9.62	6.34	5.80	7.33	10.86	6.37	8.25	6.34	7.21	11.79
12	4.24	7.03	6.20	6.90	7.96	8.66	5.30	6.67	7.50	5.11	7.09	12.05	5.74	8.06
24	2.36	3.43	1.88	3.12	4.76	2.53	2.19	2.61	2.85	2.66	2.85	6.53	2.29	3.08
36	1.17	2.03	0.92	1.56	3.27	0.95	1.47	1.14	1.73	1.48	1.38	3.31	1.33	1.69
48	0.70	1.17	0.61	1.02	2.06	0.49	0.71	0.94	0.90	1.07	0.92	1.72	0.81	1.03
60	0.49	0.50	0.43	0.66	1.77	0.31	0.74	0.81	0.58	0.69	0.55	0.81	0.54	0.74
72	BLOQ	BLOQ	0.30	0.49	1.48	BLOQ	0.49	0.54	0.34	0.52	0.40	BLOQ	0.35	0.40

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The bioavailability, as measured by the extent of absorption (AUC) indicates, that 3 capsules of Example 1 of the present invention (201 mg of fenofibrate AUC = 195) are bioequivalent to 3 capsules of the conventional form (300 mg of fenofibrate AUC = 221).

That is, the bioavailability of fenofibrate from the composition of Example 1 of the present invention is 1.5 times higher than the bioavailability of fenofibrate of the conventional form.

10

## EXAMPLE 2

Fenofibrate	5 kg
Gelucire® 44/14	7.5 kg
Carbowax 20,000	1.5 kg
Hydroxypropylcellulose	<u>2.5 kg</u>
	16.5 kg

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To a heated kettle, 7.5 kg of Gelucire® 44/14 and 1.5 kg of carbowax 20,000 were added and then heated at 85°C until all components are molten. 5 kg of fenofibrate was added slowly while continuously stirring. When all the fenofibrate was dissolved, 2.5 kg of hydroxypropylcellulose was added and agitation was maintained for about twenty minutes. Using a liquid filling capsule machine with dosing pumps heated at 85°C, capsules of size 0 were filled with 660 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so

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prepared contained 200 mg of fenofibrate. 12,701 capsules were produced and individually weighed. Results of the capsule weighing is shown in Table 3.

TABLE 3 Capsules Weight Variations From 12,701 Capsules		
5	Theoretical Weight	764.5 mg
	Mean weight of acceptable capsules (95-105%)	763.9 mg
	Standard Deviation of Accepted Capsules	6.9 mg
10	Relative Standard Deviation of Accepted Capsules	0.9%
	Percent of Rejected Capsules (below 95% of Theoretical Amount)	0.307%
15	Percent of Rejected Capsules (above 105% of Theoretical Amount)	0.039%

It may readily be appreciated from Table 3 that the filling process of the present invention is extremely accurate.

#### PHARMACOKINETICAL STUDY

The composition of Example 2 of the present invention was compared during a Pharmacokinetical study to the co-micronized formulation available on the French market (Lypanthyl 200 M®).

The study was conducted as a single dose, randomized, four-way cross over study in 8 healthy subjects. The

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subjects were randomly assigned to one of four administration sequences. On each of the four sessions, separated by wash-out periods of 7 days, the subjects received either 200 mg of fenofibrate under the form

5   Lypantyl 200 M® or 200 mg of fenofibrate under the form of Example 2 with and without a high-fat breakfast. Blood samples were taken before and at different times up to 72 hours after administration. The plasma concentrations of fenofibric acid was determined in the samples using on HPLC

10   Method..

The pharmacokinetics parameters obtained are shown in Table 4.

15   

TABLE 4 Pharmacokinetical Parameters After Administration of Lypantyl 200 M® and Composition of Example 2 Taken With and Without a High Fat Breakfast (Dose 200 mg of Fenofibrate)				
	Without Food		With Food	
	Example 2	Lipanthyl 200M®	Example 2	Lipanthyl 200M®
AUC <sub>0-72</sub>	107.0	101.0	181.0	184.7
C <sub>max</sub>	5.1	5.9	11.1	10.9
T <sub>max</sub>	5.9	5.2	5.2	5.7

20   The present composition may thus be advantageously used to treat hyperlipidemia and/or hypercholesterolemia in humans. Generally, the effective daily amount of fenofibrate from humans ranges from about 100 mg to 600 mg per day, and preferably from about 100 to 300 mg per day,

25   with the precise amount being determined by the attending

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physician, considering such parameters as condition severity and body weight, for example.

Having fully described the present invention, it will be apparent to one of ordinary skill in the art that many  
5 changes and modification may be made to the above-described embodiments without departing from the spirit and scope of the present invention.

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CLAIMS

1. A pharmaceutical composition for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which comprises an effective amount of each of fenofibrate and an excipient comprising one or more polyglycolized glycerides.

2. The composition of Claim 1, wherein said fenofibrate is present in an amount of 5% to 95% by weight based on the total weight of the composition.

3. The composition of Claim 1, wherein the polyglycolized glycerides have a HLB value of at least 10.

4. The composition of Claim 3, wherein the polyglycolized glycerides have a HLB value of from 12 to 15.

5. The composition of Claim 1, which further comprises polyalkylene glycols to adjust the HLB value or melting point or both to the desired value.

6. The composition of Claim 1, wherein a suspension stabilizer is added.

7. The composition of Claim 6, wherein said suspension stabilizer is selected from the group and consisting of cellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene) bloc polymers.

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8. The composition of Claim 1, in which said fenofibrate and said excipient are in unit dosage form and are contained in a hard gelatin capsule.

9. The composition of Claim 8, wherein said hard  
5 gelatin capsule contains from about 67 mg to about 200 mg of fenofibrate.

10. A method of making a solid oral dosage form of a pharmaceutical composition, comprising an effective amount of each of fenofibrate and an excipient comprising one or  
10 more polyglycolyzed glycerides, which method comprises adding said molten fenofibrate and said excipient to hard gelatin capsules, and allowing said said molten fenofibrate and said excipient to cool therein.

11. A method of treating hyperlipidemia or  
15 hypercholesterolemia or both in a mammal in need thereof, which comprises administering to said mammal an effective amount of a pharmaceutical composition, comprising fenofibrate and an excipient containing one or more polyglycolyzed glycerides.

20 12. The method of Claim 11, wherein said mammal is human, and said effective amount of fenofibrate in said composition is from about 100 mg to 600 mg per day.

13. The method of Claim 12, wherein said effective  
amount of fenofibrate in said composition is from about 100  
25 mg to 300 mg per day.

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14. The method of Claim 11, wherein said composition is administered orally.

15. The method of Claim 10, which is with the proviso that the fenofibrate used is not co-micronized.

# INTERNATIONAL SEARCH REPORT

National Application No

PCT/BE 96/00002

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A61K31/22 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 24893 (R. P. SCHERER LTD.) 21 September 1995 see claim 1 see page 13, line 5 - page 15, line 7 see page 25, line 3 - line 4 see page 44; example 6 -----	1-4,6-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \* & \* document member of the same patent family

Date of the actual completion of the international search

29 March 1996

Date of mailing of the international search report

11. 04. 96

Name and mailing address of the ISA  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax ( + 31-70) 340-3016

Authorized officer

Ventura Amat, A

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/BE 96/00002

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 11-14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

### Information on patent family members

Internal Application No

PCT/BE 96/00002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0-A-9524893	21-09-95	AU-B- 1897495	03-10-95
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## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>V 358.170</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/BE 96/ 00002</b>	International filing date (day/month/year) <b>10/01/96</b>	(Earliest) Priority Date (day/month/year) <b>10/01/95</b>
Applicant <b>GALEPHAR P.R. INC. et al.</b>		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES**

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 11-14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/BE 96/00002

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/22 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 24893 (R. P. SCHERER LTD.) 21 September 1995 see claim 1 see page 13, line 5 - page 15, line 7 see page 25, line 3 - line 4 see page 44; example 6 -----	1-4,6-15

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

Ventura Amat, A

# INTERNATIONAL SEARCH REPORT

Information on patent family members

**Information on patent family members**

International Application No

PCT/BE 96/00002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9524893	21-09-95	AU-B- 1897495	03-10-95
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## PATENT COOPERATION TREATY

26 JUL. 1996

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE  
COMMUNICATION OF THE INTERNATIONAL  
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

SCHMITZ, Y.  
Gevers Patents  
Holidaystraat 5  
B-1831 Diegem  
BELGIQUE

Date of mailing (day/month/year) 18 July 1996 (18.07.96)		IMPORTANT NOTICE	
Applicant's or agent's file reference V 358.170			
International application No. PCT/BE96/00002	International filing date 10 January 1996 (10.01.96)	Priority date 10 January 1995 (10.01.95)	
Applicant GALEPHAR P.R. INC. et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AT,AU,BR,CA,CN,CZ,DE,EP,FI,GB,JP,KP,KR,NO,NZ,PL,RO,RU,SK,US

2. In accordance with Rule 47.1(c), third sentence, each designated Office will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Offices.
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
18 July 1996 (18.07.96) under No. WO 96/21439

## REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

## REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 730.91.11
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NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF  
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year) 18 July 1996 (18.07.96)	IMPORTANT NOTICE
Applicant's or agent's file reference V 358.170	International application No. PCT/BE96/00002
<p>The designated Office(s) of:</p> <p>AL,AM,AP,AZ,BB,BG,BY,CH,DK,EA,EE,ES,GE,HU,IS,KE,KG,KZ,LK,LR,LS,LT,LU,LV,MD,MG,MK, MN,MW,MX,OA,PT,SD,SE,SG,SI,TJ,TM,TR,TT,UA,UG,UZ,VN</p> <p>has (have) waived the requirement for such a communication, but nevertheless a copy of the international application need not be furnished by the applicant to the Office(s) concerned.</p>	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>A61K 31/22, 9/48</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 96/21439</b> (43) International Publication Date: 18 July 1996 (18.07.96)</p>
<p>(21) International Application Number: <b>PCT/BE96/00002</b> (22) International Filing Date: 10 January 1996 (10.01.96) (30) Priority Data: 08/370,883 10 January 1995 (10.01.95) US (71) Applicant (for all designated States except US): <b>GALEPHAR P.R. INC. [VC/US]; Ave Iturregui Calle B, P.O. Box 3468, Carolina, Puerto Rico 00984-3468 (US).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>DEBOECK, Arthur, M. [BE/US]; HC02 Box 14885, Gurabo, Puerto Rico 00778 (US). BAUDIER, Philippe [FR/BE]; Avenue Blucher 10, B-1410 Waterloo (BE). MAES, Paul, J. [BE/BE]; Rue Robert Ledecq 8, B-1440 Wauthier-Braine (BE).</b> (74) Agents: <b>SCHMITZ, Y. et al.; Gevers Patents, Holidaystraat 5, B-1831 Diegem (BE).</b></p>		<p>(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> With international search report.</p>
<p>(54) Title: <b>PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES</b> (57) Abstract  A pharmaceutical composition is provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.</p>		

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/22, 9/48</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/21439</b> <b>(43) International Publication Date:</b> 18 July 1996 (18.07.96)
<b>(21) International Application Number:</b> PCT/BE96/00002 <b>(22) International Filing Date:</b> 10 January 1996 (10.01.96) <b>(30) Priority Data:</b> 08/370,883 10 January 1995 (10.01.95) US <b>(71) Applicant (for all designated States except US):</b> GALEPHAR P.R. INC. [VC/PR]; Ave Iturregui Calle B, P.O. Box 3468, Carolina, Puerto Rico 00984-3468 (PR). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DEBOECK, Arthur, M. [BE/PR]; HC02 Box 14885, Gurabo, Puerto Rico 00778 (PR). BAUDIER, Philippe [FR/BE]; Avenue Blucher 10, B-1410 Waterloo (BE). MAES, Paul, J. [BE/BE]; Rue Robert Ledecq 8, B-1440 Wauthier-Braine (BE). <b>(74) Agents:</b> SCHMITZ, Y. et al.; Gevers Patents, Holidaystraat 5, B-1831 Diegem (BE).		<b>(81) Designated States:</b> AL, AM, AT, AT (Utility model), AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES**(57) Abstract**

A pharmaceutical composition is provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.

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GA	Gabon			VN	Viet Nam

- 1 -

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE  
AND POLYGLYCOLIZED GLYCERIDES

BACKGROUND OF THE INVENTION

5 Field of the Invention:

The present invention relates to a pharmaceutical dosage form of fenofibrate having enhanced bioavailability, as well as to an advantageous process for making the same.

Description of the Background:

10 Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 300 mg which is administered in two or three doses.

15 Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted  
20 predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate, is presently available in a pharmaceutical dosage form consisting of hard gelatin  
25 capsules containing fenofibrate, lactose starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is

-2-

effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity. (Strolin & Al, Act Pharmacol. Toxicol. 1986; 59 (Suppl. 5); 167).

5       The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor and Al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M 1944CS) with HLB of between 3-4. In order to use the  
10       product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in  
15       bioavailability between this liquid formulation and the conventional form when the product was given with food.

European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl  
20       sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrrolidone and magnesium stearate. A formulation of this composition is actually available on the French market  
25       under the trade name Lypantyl 200 M®. A study comparing this formulation (Lypantyl 200 M®) to the conventional form

-3-

was undertaken and a statistically significant increase in bioavailability was indicated for the former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form. (J.L. Suichard & Al Cun Therapeutic Research Vol. 54, NS, Nov. 1993).

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

#### SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a fenofibrate formulation not requiring use of co-micronization which, nevertheless, exhibits a

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bioavailability comparable to formulations of fenofibrate which do.

It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate  
5 formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

The above objects and others are provided by a pharmaceutical composition for treating hyperlipidemia in  
10 and/or hypercholesterolemia a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a pharmaceutical  
15 formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of each of a fenofibrate composition and an excipient which contains one or more polyglycolized glycerides, the polyglycolized glycerides preferably having  
20 an HLB value of at least about 10.

The present invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is soluble, whereby particle size  
25 specifications are not required.

-5-

The present invention also relates to the addition of a suspension stabilizer to the molten solution of fenofibrate-polyglycolized glycerides. The suspension stabilizer avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene) bloc polymers. Other suspension stabilizers equivalent to these stabilizers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous fenofibrate solution is filled in hard gelatin capsules. This filling process permits the obtention of very precise fenofibrate amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

-6-

Polyglycolized glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean  
5 relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component  
10 contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably  
15 contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire®.

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more  
20 preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18°C and 60°C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30°C, and preferably above 35°C, since there is no need for  
25 sealing the capsule, to assure the leak proofness thereof, when such excipients are used.

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Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The HLB value and melting point of the composition may further be adjusted with the  
5 addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

10 It has also been discovered that the present composition affords an increased bioavailability of the fenofibrate as compared to conventional formulations.

Although the present inventors do not wish to be bound by any particular theories, one plausible mechanism of  
15 operation for the present invention is that upon cooling, the melted mixture of hot fenofibrate-polyglycolized glycerides maintains the fenofibrate in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the  
20 fenofibrate due to the HLB value of the excipient mixture, whereby fenofibrate is readily absorbed.

Generally, the composition of the present invention contains from about 5% to 95% by weight of fenofibrate and from about 95% to 5% by weight of excipient including one  
25 or more polyglycolized glycerides. It is preferred, however, if the present composition contains from about 20%

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to 80% by weight of fenofibrate and from about 80% to 20% by weight of excipient. It is even more preferred, however, if the present composition contains from about 30% to 70% by weight of fenofibrate and from about 70% to 30% by weight of excipient.

In a particularly preferred composition, generally about 45% to 55% by weight of fenofibrate is used and about 55% to 45% by weight of excipient containing the one or more polyglycolized glycerides is used.

Generally, the method of the present invention entails adding one or more excipients, including the one or more polyglycolized glycerides to containing means and then heating the excipients until all components are melted. Then, fenofibrate is added slowly with continuous stirring until all fenofibrate added is dissolved. Stirring is then continued for about 10 minutes to about 1 hour, and preferably for about 15 minutes to about 30 minutes. Then, containing means for the pharmaceutical composition, such as hard gelatin capsules, are filled with the composition using a liquid filing capsule machine having dosing pumps which are heated to the same temperature as the temperature of the molten pharmaceutical composition. Generally, this temperature is about 55°C to about 95°C, more typically in the range of about 80°C to 90°C. Upon cooling to ambient temperature, the capsules are packed in bottles. When

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capsules of size 3 are used, each capsule so prepared contains 67 mg of fenofibrate.

It is advantageous, however, to use the following protocol. To about 3 parts by weight polyglycolized glyceride excipient having a melting point of 44°C and an HLB value of 14 molten at 80°C, is added about 2 parts by weight of fenofibrate and about 1 part by weight of hydroxypropyl cellulose. After maintaining the solution under agitation for about 20 additional minutes, hard gelatin capsules are filled therewith.

The present invention will now be further described by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

15

## EXAMPLE 1

Fenofibrate	6.7 kg
Gelucire® 44/14	5.0 kg
Polyoxamer 407	<u>5.0 kg</u>
	16.7 kg

20

In a stainless steel container, were introduced 5 kg of Gelucire® 44/14 and 5 kg of Poloxamer 407, which were then heated at 85°C until all components are molten. 6.7 kg of fenofibrate was added slowly while continuously stirring the mixture. When all of the fenofibrate was dissolved agitation was maintained for about twenty

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minutes. Using a liquid filling capsule machine with dosing pumps heated at 85°C, capsules of size 3 was filled with 167 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so  
5 prepared contained 67 mg of fenofibrate.

#### PHARMACOKINETICAL STUDY

The composition of Example 1 was compared to conventional form in a pharmacokinetical study with 15 healthy subjects. Each subject received 3 capsules of  
10 composition of Example 1 (201 mg of fenofibrate) or 3 capsules of Lypantyl 100<sup>®</sup> (300 mg of the conventional form). The sessions were separated by a wash out period of 7 days. The medications were taken after a high-fat  
breakfast. Blood samples were obtained before and at  
15 different times up to 72 hours after administration. The plasma concentration of fenofibric acid was determined in all available samples using a conventional HPLC method.

Post-dose time (h)	Plasma Fenofibric Acid Concentration (mg./l. vs. time (h) After Administration at 3 Capsules of Example 1 (Total amount of Fenofibrate administered: 201 mg)															Mean*	SD
	2	2	3	4	5	6	8	9	10	11	12	13	14	15	16		
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	0	-
1	BLOQ	BLOQ	0.42	BLOQ	0.52	0.81	0.29	BLOQ	0.32	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	0.21	0.30
2	0.36	0.34	3.87	4.31	5.10	6.00	4.66	6.46	2.56	BLOQ	0.99	1.09	3.84	3.03	0.75	2.89	2.19
3	3.31	1.06	7.52	8.12	12.80	7.68	7.50	7.27	6.55	2.51	3.83	3.22	12.68	6.73	5.62	6.43	3.37
4	4.06	2.70	6.02	10.87	13.56	8.27	9.42	8.93	8.16	4.46	5.35	5.23	13.93	7.17	9.61	7.85	3.33
5	4.06	5.49	6.61	10.84	12.65	6.99	9.64	11.70	9.65	6.49	7.42	5.46	14.41	8.53	11.08	8.73	2.99
6	4.32	7.17	6.42	10.68	12.34	6.32	12.19	16.75	11.64	9.75	12.16	5.76	15.68	9.95	13.70	10.32	3.71
7	3.82	7.60	4.28	8.50	11.75	5.68	8.93	8.45	11.43	8.89	11.41	3.74	7.60	9.06	10.72	8.12	2.71
9	4.74	6.83	3.71	6.28	9.61	4.27	8.12	6.19	9.97	6.80	8.79	3.57	7.41	6.42	8.70	6.76	2.05
12	5.61	8.07	2.36	5.66	8.08	3.49	7.05	4.70	7.78	5.00	7.00	6.25	3.75	4.83	6.49	5.74	1.73
24	2.57	3.56	0.85	2.48	4.70	1.39	2.51	1.83	3.40	2.19	2.32	2.30	3.67	2.39	2.64	2.59	0.97
36	1.24	1.53	0.61	1.64	3.01	0.63	1.73	1.16	2.38	1.42	1.64	1.24	1.74	1.26	1.26	1.50	0.61
48	0.80	0.76	0.27	0.98	2.13	0.29	1.05	0.95	1.54	1.06	1.10	0.63	1.33	0.73	0.88	0.97	0.47
60	0.55	0.70	BLOQ	0.64	1.43	0.28	0.73	0.43	0.88	0.73	0.92	0.28	0.78	0.48	0.70	0.64	0.33
72	0.40	0.52	BLOQ	0.50	1.21	BLOQ	BLOQ	0.38	0.68	0.51	0.53	BLOQ	0.62	BLOQ	0.39	0.38	0.34

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Plasma Fenofibric Acid Concentration (mg./l vs. time (h) After Administration at 3 Capsules of the Conventional Form [Total amount of Fenofibrate administered: 300 mg]														
Post- dose time (h)	1	2	3	4	5	6	8	5	10	11	12	13	14	16
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
1	BLOQ	BLOQ	BLOQ	0.25	BLOQ	BLOQ	1.90	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
2	BLOQ	BLOQ	0.25	4.67	0.34	1.52	5.83	BLOQ	BLOQ	0.42	0.63	BLOQ	BLOQ	1.28
3	1.76	0.99	2.16	7.39	4.51	3.72	5.89	2.45	1.53	1.71	1.55	1.03	1.40	3.79
4	3.24	4.62	5.57	9.13	8.83	5.00	5.76	5.12	6.54	4.37	3.58	3.47	4.75	5.08
5	4.53	10.24	12.20	12.16	10.43	4.77	6.57	11.97	12.91	4.93	6.94	4.22	6.40	11.35
6	8.77	17.36	12.93	12.08	13.18	5.66	6.62	14.17	18.00	9.03	11.45	4.30	11.12	17.47
7	4.75	11.92	12.12	10.71	11.36	4.84	5.90	12.31	14.42	8.08	10.58	4.17	13.21	16.35
9	3.64	8.21	9.29	8.39	9.62	6.34	5.80	7.33	10.86	6.37	8.25	6.34	10.22	11.79
12	4.24	7.03	6.20	6.90	7.96	8.66	5.30	6.67	7.50	5.11	7.09	12.05	9.16	8.06
24	2.36	3.43	1.88	3.12	4.76	2.53	2.19	2.61	2.85	2.66	2.85	6.53	4.92	3.08
36	1.17	2.03	0.92	1.56	3.27	0.95	1.47	1.14	1.73	1.48	1.38	3.31	2.31	1.69
48	0.70	1.17	0.61	1.02	2.06	0.49	0.71	0.94	0.90	1.07	0.92	1.72	1.39	1.03
60	0.49	0.50	0.43	0.66	1.77	0.31	0.74	0.81	0.58	0.69	0.55	0.81	1.13	0.74
72	BLOQ	BLOQ	0.30	0.49	1.48	BLOQ	0.49	0.54	0.34	0.52	0.40	BLOQ	0.83	0.40

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The bioavailability, as measured by the extent of absorption (AUC) indicates, that 3 capsules of Example 1 of the present invention (201 mg of fenofibrate AUC = 195) are bioequivalent to 3 capsules of the conventional form (300 mg of fenofibrate AUC = 221).

That is, the bioavailability of fenofibrate from the composition of Example 1 of the present invention is 1.5 times higher than the bioavailability of fenofibrate of the conventional form.

10

## EXAMPLE 2

Fenofibrate	5 kg
Gelucire® 44/14	7.5 kg
Carbowax 20,000	1.5 kg
Hydroxypropylcellulose	<u>2.5 kg</u>
	16.5 kg

15

To a heated kettel, 7.5 kg of Gelucire® 44/14 and 1.5 kg of carbowax 20,000 were added and then heated at 85°C until all components are molten. 5 kg of fenofibrate was added slowly while continuously stirring. When all the fenofibrate was dissolved, 2.5 kg of hydroxypropylcellulose was added and agitation was maintained for about twenty minutes. Using a liquid filling capsule machine with dosing pumps heated at 85°C, capsules of size 0 were filled with 660 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so

25

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prepared contained 200 mg of fenofibrate. 12,701 capsules were produced and individually weighed. Results of the capsule weighing is shown in Table 3.

TABLE 3 Capsules Weight Variations From 12,701 Capsules		
5	Theoretical Weight	764.5 mg
	Mean weight of acceptable capsules (95-105%)	763.9 mg
	Standard Deviation of Accepted Capsules	6.9 mg
10	Relative Standard Deviation of Accepted Capsules	0.9%
	Percent of Rejected Capsules (below 95% of Theoretical Amount)	0.307%
15	Percent of Rejected Capsules (above 105% of Theoretical Amount)	0.039%

It may readily be appreciated from Table 3 that the filling process of the present invention is extremely accurate.

#### PHARMACOKINETICAL STUDY

The composition of Example 2 of the present invention was compared during a Pharmacokinetical study to the co-micronized formulation available on the French market (Lypanthyl 200 M®).

The study was conducted as a single dose, randomized, four-way cross over study in 8 healthy subjects. The

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subjects were randomly assigned to one of four administration sequences. On each of the four sessions, separated by wash-out periods of 7 days, the subjects received either 200 mg of fenofibrate under the form

5 Lypantyl 200 M® or 200 mg of fenofibrate under the form of Example 2 with and without a high-fat breakfast. Blood samples were taken before and at different times up to 72 hours after administration. The plasma concentrations of fenofibric acid was determined in the samples using on HPLC

10 Method...

The pharmacokinetics parameters obtained are shown in Table 4.

15

TABLE 4 Pharmacokinetical Parameters After Administration of Lypantyl 200 M® and Composition of Example 2 Taken With and Without a High Fat Breakfast (Dose 200 mg of Fenofibrate)				
	Without Food		With Food	
	Example 2	Lipanthyl 200M®	Example 2	Lipanthyl 200M®
AUC <sub>0-72</sub>	107.0	101.0	181.0	184.7
C <sub>max</sub>	5.1	5.9	11.1	10.9
T <sub>max</sub>	5.9	5.2	5.2	5.7

20 The present composition may thus be advantageously used to treat hyperlipidemia and/or hypercholesterolemia in humans. Generally, the effective daily amount of fenofibrate from humans ranges from about 100 mg to 600 mg per day, and preferably from about 100 to 300 mg per day,

25 with the precise amount being determined by the attending

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physician, considering such parameters as condition severity and body weight, for example.

Having fully described the present invention, it will be apparent to one of ordinary skill in the art that many  
5 changes and modification may be made to the above-described embodiments without departing from the spirit and scope of the present invention.

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CLAIMS

1. A pharmaceutical composition for treating hyperlipidemia or hypercholesterolemia or both in a mammal,  
5 which comprises an effective amount of each of fenofibrate and an excipient comprising one or more polyglycolized glycerides.
2. The composition of Claim 1, wherein said fenofibrate is present in an amount of 5% to 95% by weight  
10 based on the total weight of the composition.
3. The composition of Claim 1, wherein the polyglycolized glycerides have a HLB value of at least 10.
4. The composition of Claim 3, wherein the polyglycolized glycerides have a HLB value of from 12 to  
15 15.
5. The composition of Claim 1, which further comprises polyalkylene glycols to adjust the HLB value or melting point or both to the desired value.
6. The composition of Claim 1, wherein a suspension  
20 stabilizer is added.
7. The composition of Claim 6, wherein said suspension stabilizer is selected from the group and consisting of cellulose, povidone, poloxamers,  $\alpha$ ,  $\Omega$ -hydroxy-poly(oxyethylene) poly(oxypropylene)-  
25 poly(oxyethylene) bloc polymers.

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8. The composition of Claim 1, in which said fenofibrate and said excipient are in unit dosage form and are contained in a hard gelatin capsule.

9. The composition of Claim 8, wherein said hard  
5 gelatin capsule contains from about 67 mg to about 200 mg of fenofibrate.

10. A method of making a solid oral dosage form of a pharmaceutical composition, comprising an effective amount of each of fenofibrate and an excipient comprising one or  
10 more polyglycolyzed glycerides, which method comprises adding said molten fenofibrate and said excipient to hard gelatin capsules, and allowing said said molten fenofibrate and said excipient to cool therein.

11. A method of treating hyperlipidemia or  
15 hypercholesterolemia or both in a mammal in need thereof, which comprises administering to said mammal an effective amount of a pharmaceutical composition, comprising fenofibrate and an excipient containing one or more polyglycolyzed glycerides.

20 12. The method of Claim 11, wherein said mammal is human, and said effective amount of fenofibrate in said composition is from about 100 mg to 600 mg per day.

13. The method of Claim 12, wherein said effective  
amount of fenofibrate in said composition is from about 100  
25 mg to 300 mg per day.

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14. The method of Claim 11, wherein said composition is administered orally.

15. The method of Claim 10, which is with the proviso that the fenofibrate used is not co-micronized.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/BE 96/00002

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/22 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO, A, 95 24893 (R. P. SCHERER LTD.) 21 September 1995 see claim 1 see page 13, line 5 - page 15, line 7 see page 25, line 3 - line 4 see page 44; example 6 -----</p>	1-4, 6-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

29 March 1996

Date of mailing of the international search report

11. 04. 96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Ventura Amat, A

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/BE 96/ 00002

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 11-14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/BE 96/00002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9524893	21-09-95	AU-B- 1897495	03-10-95
-----			

## PATENT COOPERATION TREATY

PCT 06 SEP. 1996

INFORMATION CONCERNING ELECTED  
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

SCHMITZ, Y.  
Gevers Patents  
Holidaystraat 5  
B-1831 Diegem  
BELGIQUE

Date of mailing (day/month/year) 02 September 1996 (02.09.96)		IMPORTANT INFORMATION	
Applicant's or agent's file reference V 358.170			
International application No. PCT/BE96/00002	International filing date (day/month/year) 10 January 1996 (10.01.96)	Priority date (day/month/year) 10 January 1995 (10.01.95)	
Applicant GALEPHAR P.R. INC. et al			

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, DE, DK, FR, GB, IE, IT, LU, MC, NL, PT, SE

National : AT, AU, BG, BR, CA, CH, CN, CZ, DE, FI, GB, HU, JP, KP, KR, LV, MN, NO, NZ, PL, RO, RU, SE, SK, US, VN

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : KE, LS, MW, SD, SZ, UG

EA : AZ, BY, KZ, RU, TJ, TM


OA : BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

National : AL, AM, AZ, BB, BY, DK, EE, GE, IS, KE, KG, KZ, LK, LR, LS, LT, LU, MD, MG, MK, MW, MX, PT, SD, SG, SI, TJ, TM, TR, TT, UA, UG, UZ

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of the annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent including, where applicable, ES and GR which cannot be elected since they are not bound by Chapter II.

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer:</p> <p>Céline Faust </p> <p>Telephone No. (41-22) 730.91.11</p>
---	---

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 02 September 1996 (02.09.96)	
<b>International application No.</b> PCT/BE96/00002	<b>Applicant's or agent's file reference</b> V 358.170
<b>International filing date</b> (day/month/year) 10 January 1996 (10.01.96)	<b>Priority date</b> (day/month/year) 10 January 1995 (10.01.95)
<b>Applicant</b> DEBOECK, Arthur, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

09 August 1996 (09.08.96)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b> Céline Faust Telephone No.: (41-22) 730.91.11
--	---

V 125 + 8 - V 301 + 0

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>V712287/V358170</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/ BE 96/ 00002</b>	International filing date ( <i>day/month/year</i> ) <b>10/01/1996</b>	Priority date ( <i>day/month/year</i> ) <b>10/01/1995</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K31/22</b>		
Applicant <b>GALEPHAR P.R. INC. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This **REPORT** consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>09/08/1996</b>	Date of completion of this report <b>11. 11. 96</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer <b>H. Santos-Rivero</b> <b>M. Santos-Rivero</b> Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/BE96/00002

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☒ the international application as originally filed.

☐ the description, pages \_\_\_\_\_, as originally filed,  
pages \_\_\_\_\_, filed with the demand,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the claims, Nos. \_\_\_\_\_, as originally filed,  
Nos. \_\_\_\_\_, as amended under Article 19,  
Nos. \_\_\_\_\_, filed with the demand,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
Nos. \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

☐ the drawings, sheets/fig \_\_\_\_\_, as originally filed,  
sheets/fig \_\_\_\_\_, filed with the demand,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_,  
sheets/fig \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

2. The amendments have resulted in the cancellation of:

☐ the description, pages \_\_\_\_\_.  
☐ the claims, Nos. \_\_\_\_\_.  
☐ the drawings, sheets/fig \_\_\_\_\_.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/BE96/00002

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-14\_\_\_\_\_

because:

☒ the said international application, or the said claims Nos. 11-14\_\_\_\_\_ relate to the following subject matter which does not require an international preliminary examination (specify):

The subject-matter of claims 11-14 relates to a method for treatment of the human or animal body. Rule 67.1(iv) PCT

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. \_\_\_\_\_ are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. \_\_\_\_\_.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-15_____	YES
	Claims _____	NO
Inventive Step (IS)	Claims 1-15_____	YES
	Claims _____	NO
Industrial Applicability (IA)	Claims 1-10, 15_____	YES
	Claims _____	NO

2. CITATIONS AND EXPLANATIONS

- 1). It is considered that the present application is entitled to the right of priority. Therefore, document WO-A-9 5 24 893 (D1) does not form part of the state of the art. R 64.1 PCT
- 2). The subject-matter of claims 1-15 is considered to be new and to involve an inventive step. Articles 33(2) and (3) PCT

The International Search Authority has not found any prior art document which discloses pharmaceutical compositions comprising fenofibrate and polyglycolized glycerides. Thus, such compositions are considered to be new.

The compositions according to the present invention present better bioavailability than those of available on the market, while its method of preparation involves far less costs, because it avoids the co-micronization

of fenofibrate, which is time consuming and difficult to obtain with a proper size. See examples 2 and 3 of the present application.

- 3). However, it is noted that document D1 discloses formulations comprising fenofibrate and polyglycolyzed glycerides. See page 25, line 4 and page 13, line 14.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.  
PCT/BE96/00002

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VII. Certain defects in the international application

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The following defects in the form or contents of the international application have been noted:

Claim 10, line 6 contains twice the word "said".

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VIII. Certain observations on the international application

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

- 1). The compounds indicated in the examples under trade mark names, should be clarified as to indicate its composition. It is noted that if the grant of a patent will be requested in the national phase, the patent may last up to 20 years and the trade names may disappear or change during this period. If so happens, then it will not be possible to repeat the examples.
- 2). In claim 11, line 4, after comprising it should be introduced the statement: "an effective amount of each" to be in agreement with claim 1. Rule 13.1 PCT
- 3). The subject-matter of claim 15 is not clear. Article 6 PCT  
According to claim 1, the fenofibrate is not co-micronized, otherwise it is understood that it would be "co-micronized fenofibrate" and not mere "fenofibrate". Further, the description never indicates that co-micronized fenofibrate is used. Thus, it is assumed that the fenofibrate used is pure.  
Therefore, the subject-matter of claim 15 is superfluous and confusing and should be deleted.

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 15.11.96

PCT

Applicant's or agent's file reference <b>V712287/V358170</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/BE 96/ 00002</b>	International filing date (day/month/year) <b>10/01/1996</b>	Priority date (day/month/year) <b>10/01/1995</b>
International Patent Classification (IPC) or national classification and IPC <b>A61K31/22</b>		
Applicant <b>GALEPHAR P.R. INC. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This **REPORT** consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of \_\_\_\_\_ sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand <b>09/08/1996</b>	Date of completion of this report <b>11.11.96</b>
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer <b>H. Santos-Rivero</b> <b>M. Santos-Rivero</b> Telephone No.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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The subject-matter of claims 11-14 relates to a method for treatment of the human or animal body. Rule 67.1(iv)  
PCT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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## PATENT COOPERATION TREATY

PCT

COMMUNICATION OF  
INTERNATIONAL APPLICATIONS

(PCT Article 20)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as designated Office

Date of mailing:

10 October 1996 (10.10.96)

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:

PCT/BE96/00002

International publication no.:

WO96/21439

**CORRECTED VERSION  
VERSION CORRIGEE**

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 730.91.11